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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/810,601	03/15/2001	Stephen Donovan	D-2947CIP	9283

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	14

DATE MAILED: 04/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/810,601	DONOVAN, STEPHEN	
	Examin r	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears n the c ver sheet with th c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3, 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 22 and 23 in Paper No. 6 (filed September 6, 2002) is acknowledged. The traversal is on the ground(s) that all claims are limited to an agent or use of the agent which comprises a targeting component which selectively binds to a GnRH receptor and hence a single search should surface to search all the claims. This is not found persuasive because applicant's response has not demonstrated there is no search burden. Restriction is proper when two or more claimed inventions are either independent **or** distinct. See MPEP 803. Furthermore, coexamination of each of the additional groups would have required a search of additional art areas. For example, in Group III, it would require additional searches for the disease state of precocious puberty, and in Group IV, it would require additional searches for endometriosis. Therefore, coexamination of each of these inventions would require a serious additional burden of search. In the response, applicant has canceled claims 1-21 and 24-25. Therefore, claims 22 and 23 are examined.

2. Sequence Listing filed February 27, 2003 is acknowledged. CRF has been entered.

Claim Objections

3. Claim 23 is objected to because the claim contains non-elected diseases such as endometriosis and precocious puberty.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a specific gonadotrophin related disease such as prostate cancer, breast cancer or endometrial cancer in a mammal comprising administering an agent of a botulinum toxin (or, a butyricum toxin or a tetani toxin) component covalently coupled to GnRH or a functional GnRH analog, wherein the toxin component is the LH_N; or administering an agent of the conjugate of a hybrid botulinum toxin and a GnRH as indicated in the prior art, does not reasonably provide enablement for a method of treating all gonadotrophin related diseases (e.g., precocious puberty) and where the administered agent comprises a light chain component of a botulinum toxin, a butyricum toxin or a tetani toxin; a translocation component of a botulinum toxin, a butyricum toxin or a tetani toxin; and a targeting component which selectively binds to a GnRH receptor, wherein the disease, the fragment or the variant of the light chain, the modified heavy chain or the variant of heavy chain, and the targeting component are not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 22 and 23 encompass a method of treating a gonadotrophin related disease comprising administering an agent, wherein the agent comprises a light chain component of a botulinum toxin, a butyricum toxin or a tetani toxin; a translocation component of a botulinum toxin, a butyricum toxin or a tetani toxin; and a targeting component which selectively binds to a gnRH receptor. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that an agent comprising a light chain component of a botulinum toxin, a butyricum toxin or a tetani toxin; a translocation component of a botulinum

toxin, a butyricum toxin or a tetani toxin; and a targeting component which selectively binds to a GnRH receptor, can be used for treating a gonadotrophin related disease (pages 22-23). There are no indicia that the present application enables the full scope in view of a method of treating a gonadotrophin related disease using the agent as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the gonadotrophin related diseases, the light chain component such as the fragment or the variant, the translocation component such as the modified heavy chain or the variant, and the targeting component such as variable region of an antibody, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for the agent of LH_N (from BT)-GnRH used for treating prosate cancer, endometrial cancer and breast cancer (Examples 2, 4 and 5). In Example 3, treatment of precocious puberty has been described. However, there is no specific dose indicated, the

example only indicates the dose used is sufficient to reduce the patient's level of circulating gonadotrophin by 80% to 30%, preferably by 50%. Since there is no in vitro data indicated, a person skilled in the art is not able to extrapolate the dose from in vitro to in vivo. Furthermore, there is no animal model for the disease state presented, thus it is not apparent what dose is needed for the treatment. Moreover, the specification also indicates the amount of agents administered can vary widely according to the particular disorder being treated (page 35, lines 4-6), therefore the dose used for treating cancers cannot be applied to the treatment of precocious puberty.

(3). The state of the prior art and relative skill of those in the art:

The prior art (the combined references of Nett *et al.*, U. S. Patent 5,707,964 and Johnson *et al.*, U. S. Patent 5,939,070; See paragraph 6 shown below) indicates a conjugate of a hybrid botulinum toxin and a GnRH can be used for treating prostate cancer or breast cancer. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific teachings on identities of the fragment or the variant of the light chain, the variant of the translocation component, the modified heavy chain, and the targeting component besides a GnRH in the agent, and the treating conditions for treating various gonadotrophin related diseases using the agent to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

Claims 22 and 23 are directed to a method of treating a gonadotrophin related disease comprising administering an agent, wherein the agent comprises a light chain component; a translocation component; and a targeting component which selectively binds to a GnRH

receptor. The specification indicates an agent comprising a light chain component of a botulinum toxin, a butyricum toxin or a tetani toxin; a translocation component of a botulinum toxin, a butyricum toxin or a tetani toxin; and a targeting component which selectively binds to a GnRH receptor, can be used for treating a gonadotrophin related disease (pages 22-23). However, the specification only demonstrates using LH_N-GnRH for treating gonadotrophin related cancers (Examples 2, 4 and 5), but fails to identify any fragment or variant of light chain, any modified heavy chain besides H_C removed from heavy chain, or the variant of translocation component, the targeting component besides GnRH or GnRH analog in the agent, and to provide any example of using these agents. Moreover, the specification has not shown the treating conditions such as the dosage, the time, and the frequency of the treatment as well as the effects of these agents. There are no working examples indicating the claimed method except for treating gonadotrophin related cancers with LH_N-GnRH (See item 2 above regarding inadequate teachings in Example 3). Since the specification fails to provide sufficient teachings on identities of various toxin components and targeting component in the agent and the treating conditions of these toxins, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of these agents.

(5). Predictability or unpredictability of the art:

The claims encompass a method of treating a gonadotrophin related disease comprising administering an agent comprising a light chain component, a translocation component, and a targeting component which selectively binds to a GnRH receptor, however, the treating conditions for these conjugates are not adequately described in the specification, the invention is highly unpredictable regarding the outcome of the treatment.

(6). Nature of the Invention

The scope of the claims encompasses a method of treating gonadotrophin related disease comprising administering an agent of a light chain component, a translocation component, and a targeting component which selectively binds to a GnRH receptor, but the specification does not demonstrate using an agent containing a light chain fragment or variant, a heavy chain variant, and a targeting component besides GnRH or GnRH analog. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broader than the enabling disclosure. The working examples do not demonstrate the outcome of the treatment which is unpredictable, and the guidance and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the treatment using the agent.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 23 are indefinite because the claims lack essential steps in the method of treating a gonadotrophin related illness. The omitted step is the outcome of the treatment. Claim 23 is included in the rejection for being dependent on a rejected claim and does not correct the deficiency of the claim from which it depends. Claim 22 is also indefinite because of the use of

the term "a fragment thereof", "variants thereof" or "a modified heavy chain". The term "a fragment thereof", "variants thereof" or "a modified heavy chain" renders the claim indefinite, it is unclear what amino acid sequence the fragment has, how different the variant is as compared to the parent peptide, and how heavy chain is modified.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nett *et al.* (U. S. Patent 5,707,964) in view of Johnson *et al.* (U. S. Patent 5,939,070).

Nett *et al.* teach a conjugate of GnRH or GnRH analog with a bacterial toxin or plant toxin (e.g., diphtheria toxin, ricin toxin or pseudomonas exotoxin), and methods of treating gonadotrophin related diseases such as prostate cancer or breast cancer (column 5, line 49-column 6, line 4). Some of the toxins can be a whole molecule which has at least a toxic domain, a translocational domain and a cell binding domain, or a modified molecule which has one or more of these domains are removed (column 6, lines 5-27, Table I). However, Nett *et al.* do not disclose using the toxin component from botulinum toxin, butyricum toxin or tetani toxin to make conjugate. Johnson *et al.* disclose preparation of a hybrid botulinal toxin comprising heavy and light chains that are from different serotypes (column 4, lines 31-67). At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to use the hybrid botulinum toxin as disclosed by Johnson *et al.* to substitute the toxin component in the

GnRH-Toxin conjugate for treating a gonadotrophin related disease as taught by Nett *et al.* (claims 22 and 23) because the hybrid botulinum toxin has the advantage of changing the duration of action and immunogenicity of the toxin (column 11, lines 9-26 of Johnson *et al.*), which would improve the treatment. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusions

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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April 17, 2003

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